Common Chromosomal and Genetic Causes of Fetal Loss From Diagnosis to Delivery

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Kathy Hays Devary, MS, CGC
EvergreenHealth Maternal Fetal Medicine

Objectives

- Describe the etiology of common causes of fetal demise
- Discuss the prenatal and postnatal evaluations commonly completed in cases of fetal demise
- Identify support resources for families experiencing fetal demise

Introduction to Genetic Counseling

- Genetic counselors are master’s prepared healthcare professionals with experience in the areas of both medical genetics and counseling.
- Genetic counselors work as members of a healthcare team, providing risk assessment, education and support to individuals and families at risk for, or diagnosed with, a variety of inherited conditions.
- Genetic counselors also interpret genetic testing, provide supportive counseling, and serve as patient advocates.

Financial Disclosures

- No relevant financial interests to disclose

Prenatal Genetic Counseling

- Prenatal genetic counselors specialize in preconception and prenatal genetics
  - Maternal age
  - Abnormal screening results in pregnancy
  - Abnormal ultrasound findings
  - Teratogenic exposures
  - Family history of birth defects, medical or developmental conditions
  - Ethnicity-based screening
  - Parental anxiety

- Interpretation of history to assess the chance of a condition occurring or recurring
- Education about inheritance, risk, testing options, management, prevention, and resources
- Counseling to promote informed choices and adaptation to the risk or condition
Causes of Perinatal Loss

Definition Dilemma
- The definition of fetal death and stillbirth varies between professional organizations, national organizations, and international organizations.
- For This Talk:
  - Miscarriage = < 20 weeks gestation
  - Fetal demise/stillbirth = ≥ 20 weeks gestation
  - Neonatal death = < 5 weeks after delivery

Miscarriage
- Pregnancy loss prior to 20 weeks
- 10 – 25% of recognized pregnancy end in miscarriage
- Approximately 50% of these are the result of a chromosomal abnormality:
  - 45,X (Turner syndrome)
  - Triploidy
  - Trisomy 16
  - Trisomy 21
  - Trisomy 22

Causes of Multiple Miscarriages
- Unknown etiology
- Underlying maternal conditions:
  - Thrombophilia
  - Autoimmune disease
- Hereditary translocation:
  - A healthy adult that carries a balanced structural rearrangement of their chromosomes
  - This rearrangement can pass on an abnormal amount of chromosomal material that causes miscarriage or birth defects

Causes of Fetal Demise/Stillbirth
1. Unexplained
2. Fetal Growth Restriction/Placental Dysfunction
3. Abruptio Placenta
4. Infection
5. Chromosome and Genetic Abnormalities
6. Congenital Anomalies
7. Fetomaternal Hemorrhage
8. Umbilical Cord Complications
9. Hydrops Fetalis
10. Fetal Arrhythmia
11. Platelet Alloimmunization
12. Placental Disorders
13. Uterine Abnormalities
**Unexplained Demise/Stillbirth**

- 25-60% of losses ≥ 20 weeks are unexplained

- The likelihood of being unexplained increases with gestational age

- Families should be educated about this possibility when making decisions about pursuing additional evaluations and tests to determine the cause of a loss

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**Chromosomes and Loss**

Proportion of losses due to chromosomal abnormalities decreases with gestational age

- ~50% of miscarriages
- 12% of fetal demises prior to delivery
- 4% of losses during delivery
- 6% of neonatal deaths

- 0.7% of live births have a chromosomal condition
Down Syndrome

- A range of interests and abilities
  - Intellectual and developmental disabilities
    - Usually mild to moderate
- Variable health concerns
  - Hypotonia
  - Congenital heart defects

Down Syndrome (Trisomy 21)

- Fetuses with Down syndrome have an increased risk of miscarriage and demise

<table>
<thead>
<tr>
<th>Gestational Age at Amino</th>
<th>Spontaneous Fetal Demise*</th>
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<tbody>
<tr>
<td>15 – 17 weeks</td>
<td>~50%</td>
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<tr>
<td>18 weeks</td>
<td>43%</td>
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<tr>
<td>19</td>
<td>31%</td>
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<tr>
<td>20</td>
<td>25%</td>
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<tr>
<td>21 – 28 weeks</td>
<td>21-25%</td>
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*corrected for likelihood of spontaneous demise in a chromosomally normal fetus


Down Syndrome and Demise

- Cystic hygroma

Down Syndrome and Demise

- Placental dysfunction
- Congenital heart defect
- Pulmonary hypoplasia
- Gastrointestinal abnormalities
- Hematologic abnormalities
**Trisomy 18**

- Profound intellectual disability
- Multiple health concerns
  - IUGR
  - Congenital heart defects
- Limited Survival

**Trisomy 18 and Demise**

- Majority are lost to miscarriage
- Significant increase in risk of stillbirth
- Of live births with trisomy 18
  - Median survival 14.5 days
  - 55-65% survive < 1 week
  - 5 – 10% survive to 1 year
  - There are a handful that have longer survival, case reports of survival to 10 years or more

**Trisomy 13**

- Profound intellectual disability
- Multiple birth defects
  - Brain abnormalities
  - Congenital heart defects
- Very limited survival

**Trisomy 13 and Demise**

- Normal Brain
Trisomy 13 and Demise

- Holoprosencephaly

Trisomy 13 and Demise

- Brain and facial development are closely linked therefore facial cleft and proboscis occur with increased frequency

Trisomy 13 and Demise

- Majority are lost to miscarriage
- Significant increase in risk for stillbirth
- Of live births with trisomy 13
  - Median survival is 7 days
  - 91% survive less than 1 year
  - Longer survival rare, a case report of survival to adulthood
- Trisomy 13 increases the risk of preeclampsia

Turner Syndrome (45,X)

- Normal intelligence
- Short stature
- Premature ovarian failure
- Webbed neck
- Congenital heart defect

Turner Syndrome (45,X)

- 98-99% are lost to miscarriage or fetal demise
- Cystic hygroma leading to hydrops is a common cause of pregnancy loss

Turner Syndrome and Demise
Triploidy

- IUGR
- Large placenta with hydatidiform changes
  - Grape-like clusters of cysts
- Brain abnormalities
- Congenital heart defects
- 3-4 syndactyly

Causes of Triploidy

A. 2 sperm, 1 egg
B. 1 sperm, diploid egg
C. Diploid sperm, 1 egg

Triploidy and Demise

- Majority are lost to miscarriage
- Significant increase in the risk of stillbirth
- Virtually all cases of full triploidy have been stillborn or died in early neonatal period
  - There is a report in the literature of survival to 10.5 months
- Triploidy increases the risk of vaginal bleeding
- Triploidy increases the risk of preeclampsia

Congenital Anomalies

- A wide spectrum of anomalies can be seen in demises
- Anomalies can be a considered as a cause of loss if:
  - Epidemiologic data support a relationship
  - The anomaly is rare in newborns
  - Neonates with the anomaly often die
  - There is biologic plausibility
Neural Tube Defects
- Occur when the neural tube fails to close properly by 6 weeks gestation
- The upper portion of the neural tube represents the fetal brain
- The caudal portion represents the future spinal cord
- The location of the opening determines the severity of the condition

Neural Tube Defects - Anencephaly
- Absent calvaria, minimal/absent brain tissue
- Survival to term common
- Survival beyond 24 hours is rare

Neural Tube Defects - Myelomeningocele
- The spinal cord and meninges protrude from the back
- Frequently associated with hydrocephaly
- Fetal intervention is possible in a small number of cases

Encephalocele
- Herniation of cranial contents through a defect in the skull
- Prognosis dependent upon presence of neural tissue in the sac and presence of other anomalies
**Abdominal Wall Defect - Gastroschisis**
- Due to incomplete closure of the lateral folds at 6 weeks gestation
- Opening is usually to the right of the umbilical cord
- Usually an isolated defect
- The extent bowel damage plays a significant role in neonatal survival and long term outcome

**Abdominal Wall Defect - Omphalocele**
- Failure of the intestines to return to abdominal cavity at 10 weeks gestation
- Frequently associated with
  - Other birth defects
  - Chromosomal conditions
  - Genetic syndromes

**Potter Syndrome/Sequence**
- Caused by
  - renal abnormalities/agenesis
  - chronic leakage of amniotic fluid
- Severe oligohydramnios or anhydramnios leads to fetal consequences
  - Pulmonary hypoplasia
  - Compression abnormalities
  - Abnormal limb position
  - Potter facies (flattened nose, small jaw, cleft palate, flattened ears)

**Lethal Skeletal Dysplasias**
- Group of conditions affecting bone and cartilage
- Severely shortened limbs
- Small chest inhibits lung development
- Polyhydramnios is frequent
Lethal Skeletal Dysplasias

• Thanataphoric Dysplasia
• Achondrogenesis
• Osteogenesis Imperfecta Type II (brittle bones)
• Hypophosphatemia
• Campomelic Dysplasia (bent limb dysplasia)
• Short Rib Polydactyly Syndromes
• Fibrochondrogenesis
• Atelosteogenesis
• Chondrodysplasia Punctata

Lethal Skeletal Dysplasias

• Difficult to differentiate between types on ultrasound
• DNA testing and/or autopsy is required to reach a diagnosis
• Some are the result of a new mutation
• Some are inherited in an autosomal recessive manner (25% chance of recurrence)

Common Prenatal Tests

Ultrasound evaluation can detect a demise
- ~ 8 weeks – viability and dating
- 12 – 13 weeks – nuchal translucency (NT)
- 20 weeks – fetal anatomy

Common Prenatal Tests

Maternal serum screening can identify a demise
- Combined/First trimester screen (11-13wks)
- Quadruple screen (16-20 wks)
- AFP (16 – 20 wks)

Prenatal Testing Following Demise

Chorionic Villus Sampling (CVS)
- Typically 10 – 14 weeks
- Tests for chromosome conditions and some infections
Prenatal Testing Following Demise

- Amniocentesis (Amnio)
  - Typically 16 weeks or later
  - Tests for chromosome conditions and some infections

Prenatal Testing Following Demise

- Maternal blood tests can include:
  - Kleihauer-Betke (to detect fetomaternal hemorrhage)
  - CBC
  - Syphilis – if high risk or not completed earlier
  - Fasting glucose
  - Blood antibody screen
  - Thyroid testing
  - Lupus anticoagulant
  - Anticardiolipin antibodies
  - Liver function tests
  - Fibrinogen concentration
  - Thrombophilia

Postnatal Testing Following Demise

- Chromosomal testing of fetus/placenta after delivery
  - Traditional chromosome tests have a risk of culture failure due to demise

- Microarray is becoming the test of choice
  - Fetal/neonatal demise
  - Neonatal testing

Microarray

- Designed to detect extra or missing DNA
  - Can identify trisomy/monosomy
  - Can identify almost all microdeletion/microduplication syndromes

- Does not require cell culture

- Does not require a known risk for a specific syndrome

Microarray

- 15q deletion
## Postnatal Testing Following Demise

- **Pathology Evaluation**
  - Fetal/Neonatal Autopsy
    - Indicated if no chromosomal condition present
    - Can diagnose genetic syndromes
    - Can detect infections
    - Limited evaluation is possible
  - Placental Pathology
    - An essential part of fetal autopsy
    - Can detect infections
- **Research Opportunities**
  - In some circumstances donation of remains to research may be possible

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## Breaking Bad News

- **Advance Preparation**
  - Prepare yourself
  - Find a quiet location
  - Avoid interruptions

- **Build a therapeutic environment/relationship**
  - Determine how much family wants/needs to know
  - Have appropriate family/support persons present
  - Introduce yourself
  - Warn them bad news is coming
  - Touch may or may not be appropriate!

- **Communicate Well**
  - Ask what the family already knows
  - Be frank but compassionate
  - Avoid euphemisms and medical jargon
  - Allow for silence, tears
  - Have patient describe their understanding
  - Allow time
  - Provide written information if possible

- **Deal with patient and family reactions**
  - Assess and respond to the patient and family’s emotional reaction
  - Be empathetic
  - Do not argue with or criticize colleagues

- **Encourage and validate emotions**
  - Explore what the news means to patients
  - Offer realistic hope
  - Use interdisciplinary resources
  - Take care of your own needs and those of staff

*Am Fam Physician. 2001 Dec 15;64(12):1975-1979*
Resources for Families

- Explore resources at your facility
  - Grief and bereavement support
  - Spiritual care/chaplain support
  - Social work
  - Genetic counselor
  - Support groups
- Explore family’s natural support systems
  - Family and friends
  - Religious/spiritual community

Resources for Families

- Remembrance Photography
  - Now I Lay Me Down To Sleep
    https://www.nowilaymedowntosleep.org/
  - Free professional photography for family
  - International organization
  - All photographers donate their services and receive training
  - Arranged prior to delivery
  - It is possible no volunteer photographers will be available
  - NOT an emergency or on-call service
  - Website has posing poster to aid staff in photography if no professional photographer is available

Resources for Families

- Organ and tissue donation
  - Purposeful Gift http://purposefulgift.com/en/
    - Includes information on neonatal organ/tissue donation
    - Created by parents seeking opportunities to donate
  - Life Center Northwest http://www.lcnw.org/
    - Organ and tissue donation organization for Washington, Alaska, Montana, and North Idaho
Resources for Families

- Support Groups
  - The Tears Foundation
  - Share – Pregnancy and Infant Loss Support
  - First Candle
  - MISS Foundation
  - Center for Loss in Multiple Birth
    [http://www.climb-support.org/](http://www.climb-support.org/)

Resources for Families and Professionals

- Perinatal hospice/palliative care information
  [http://www.perinatalhospice.org/](http://www.perinatalhospice.org/)
  – Provides great resources and information for families and professionals
- Local children’s hospice and palliative care
  – Stepping Stones (King County)
  – Local hospice program

Questions?

Kathy Hays Devary, MS, CGC
kehdevary@evergreenhealth.com
425-899-2205